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(54) Title: AMIODARONE-CONTAINING PARENTERAL SOLUTION

(57) Abstract: The present invention provides an amiodarone parenteral solution suitable for intravenous administration without the necessity of dilution. The parenteral solution has an amiodarone concentration from 0.2 to 10 mg/ml and a buffer solution selected from the group consisting of lactate buffer, methanesulfonate buffer, or combinations thereof, the solution having a pH within the range from approximately 2.5 - 4.5.

AMIODARONE-CONTAINING PARENTERAL SOLUTION

DESCRIPTION

Technical Field

The present invention relates to an amiodarone antiarrhythmic agent and more particularly to a parenteral solution of amiodarone for intravenous infusion.

Background of the Invention

Amiodarone is a type III antiarrhythmic agent that exhibits a broad spectrum of activity. The hydrochloride salt is currently marketed in ampoules suitable for intravenous administration following dilution in dextrose (Cordarone IV, Wyeth-Ayrest). The pH range of the diluted product (measured in the lab) is from 3.8 - 4.0.

Amiodarone free base has an extremely low estimated intrinsic solubility in water (~6 ng/mL). The free base is neutral and by protonation with acid is converted to a more water-soluble trialkylammonium ion. However, the hydrochloride salt (used in the current commercial product) is not appreciably soluble in water at moderately low pH (3.8 - 4.5). Therefore, the commercial formulation contains polysorbate 80 as a surfactant to aid in dissolving and solubilizing the drug. This may be a serious drawback because glycol ethers and their derivatives such as polyethylene glycols (PEGs) or polysorbates (Tweens) are known to contribute to pain on injection, and may also induce anaphylactic reactions. Tween 80 has also been associated with cardiodepression, causing hypotension (Gough et al., "Hypotensive Action of Commercial Intravenous Amiodarone and Polysorbate 80 in Dogs," Journal of Cardiovascular Pharmacology, 1982, 375-380).

United States Patent No. 5,234,949 provides a surfactant-free amiodarone solution packaged in an ampoule suitable for intravenous parenteral administration upon dilution. The '949 Patent discloses using an acetate buffer solution (0.05 - 0.1 M) to adjust the pH of a 25 - 75 mg/ml amiodarone solution to be below 4 and more preferably within the range of 3.5 - 3.8. It also discloses that the concentration of the buffer and the choice of buffering agent are *critical* for

physical stability, i.e., precipitation or gel formation occurred when a 0.2 M acetate, 0.1 M phthalate, or 0.1 M phosphate buffer was used to solubilize the drug.

Published PCT Patent Application WO/9702031 provides a 1.5 - 8 wt % surfactant-containing amiodarone solution suitable for parenteral administration. The '031 Application
5 discloses using a non-ionic hydrophilic surfactant (e.g., Tween 80, Pluronic P94, or Cremophor EL) in combination with an acetate or phosphate buffer solution at a pH from 2.4 - 3.8 to solubilize the drug.

Neither of these references, however, discloses using lactic or methanesulfonic acid to solubilize the drug, nor do they describe the use of lactate or methanesulfonate buffer for preparing
10 a surfactant-free amiodarone formulation. In addition, they do not disclose the preparation of a surfactant-free amiodarone parenteral solution suitable for intravenous administration without the necessity of dilution.

Summary of the Invention

15 The present invention provides a surfactant-free amiodarone parenteral solution suitable for intravenous administration without the necessity of dilution. The solution contains an active ingredient of amiodarone hydrochloride in a concentration range from 0.2 - 10 mg/ml and a buffer solution selected from the group consisting of lactate buffer, methanesulfonate buffer or any combination of these two buffers. The solution should have a pH within the range of approximately
20 2.5 - 4.5. The solution can also optionally include an osmotic agent such as dextrose, mannitol, sorbitol, glycerol, amino acids such as glycine, or salts such as sodium chloride.

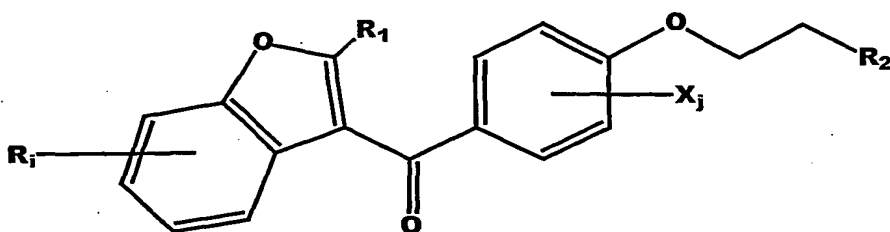
The present invention also provides a method for preparing an amiodarone solution suitable for intravenous administration. The method comprises the steps of: (1) providing an effective ingredient or ingredients of an amiodarone solution; (2) providing distilled water; (3) providing an
25 acid selected from the group consisting of lactic acid and methanesulfonic acid or combination thereof; (4) mixing an effective amount of the lactic acid, methanesulfonic acid or the combination of the two acids with heated, distilled water; (5) solubilizing an effective amount of the active ingredient in the heated water/acid solution; (6) cooling the solution; (7) adjusting the pH of the

solution with a suitable pH adjuster to be within the range of from approximately 2.5 - 4.5; (8) diluting the solution to the final active ingredient concentration. The method can include the optional step of mixing into the solution an osmotic agent such as dextrose, mannitol, sorbitol, glycerol, amino acids, inorganic salts, and any combination of these osmotic adjusters into the solution.

Detailed Description

While this invention is susceptible of embodiment in many different forms, there will herein be described in detail preferred embodiments of the invention with the understanding that the present disclosure is to be considered as an exemplification of the principles of the invention and is not intended to limit the broad aspect of the invention to the embodiments illustrated.

According to the present invention, there is provided a parenteral solution containing as an active ingredient a benzofuran drug, which is solubilized by lactic acid, methanesulfonic acid, or any combination thereof. The pH of the solution is adjusted to be within the range of approximately 2.5 - 4.5. The active ingredient has the following structural formula:



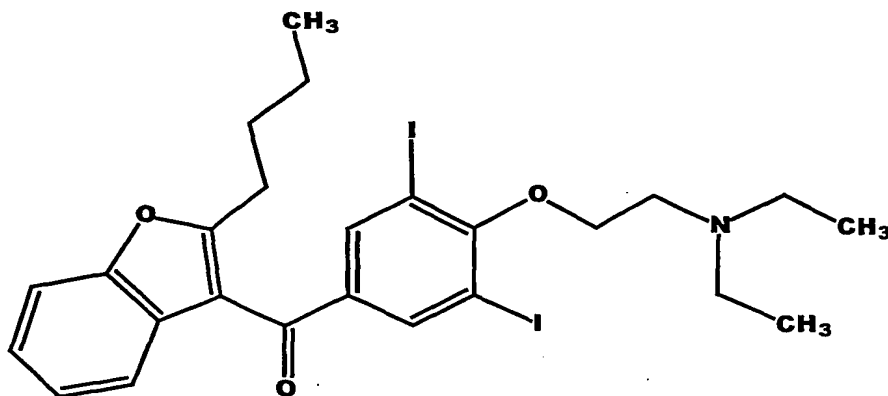
R_i represents one or more groups selected from alkyl, aryl, alkoxy, aryloxy or halogen substituents.

R_1 represents an alkyl, aryl, alkoxy, aryloxy or halogen substituent, X_j includes one or more iodo or bromo substituents on the phenyl ring. R_2 represents a dialkylamino group such as N,N-

dimethylamino or N,N-diethylamino. R₂ can also be a 1-substituted heterocycle such as 1-morpholinyl,

1-piperazinyl, or 1-piperidinyl.

In a preferred form of the invention the active ingredient is a cardiovascular agent with the following structural formula:



The parenteral solution is prepared by adding a sufficient amount of a **pH modifying solution** selected from the group consisting of **lactate buffer, lactic acid, methanesulfonate buffer and methanesulfonic acid or any combination of the same** to distilled, deionized water or Water for Injection, USP. The solution is heated to a temperature of approximately 45 - 70 °C. Amiodarone is mixed into the solution in a sufficient amount so that the concentration is from about 0.2 to 25 mg/ml, and more preferably from 0.5 to 10 mg/ml. The solution is then slightly diluted and cooled to a temperature from approximately 25 - 35 °C. An osmotic agent may be added to the solution at this point in an amount from 100 to 450 mM and more preferably from 150 to 350 mM. The solution is pH adjusted with a suitable pH adjuster (e.g., hydrochloric acid or sodium hydroxide)

to a pH from approximately 2.5 - 4.5. The solution is then diluted to give a final amiodarone concentration from 0.2 to 10 mg/ml with distilled, deionized water or Water for Injection, USP.

Suitable amiodarone hydrochloride is sold by ISOCHEM. The lactic or methanesulfonic acids may be used as the pure compounds or as solutions prepared by suitable dilutions of these acids. Lactic acid may also be heat-treated to hydrolyze any dimers or polymers present in the pure raw material, or in solutions prepared from it. Suitable lactic acid is sold by PURAC under the tradename 90% Lactic Acid, USP. Suitable methanesulfonic acid is sold by Aldrich under the tradename Methanesulfonic Acid. Suitable osmotic agents include dextrose, mannitol, sorbitol, glycerol, amino acids such as glycine, or inorganic salts such as sodium chloride.

The parenteral solutions of the present invention do not contain any non-ionic hydrophilic solubilizing surfactants, such as polyethylene glycols, polysorbates, or polyethylene glycol stearate esters which are known to have adverse pharmacologic effects when injected as a component in an I.V. solution. Nor do the formulations of the present invention contain any organic cosolvents such as propylene glycol or ethanol.

The following are non-limiting examples of the present invention and should not be used to narrow the scope of the present invention.

Example 1: Preparation of Amiodarone Formulation Using Lactic Acid

To a 20-L jacketed tank reactor was added 8 L of distilled, deionized water. To this was added 400 mL of 20% lactic acid (previously prepared by heat treatment of a diluted 90% lactic acid concentrate to hydrolyze lactic acid dimer). The mixture was brought to 55 °C. 36 g of amiodarone hydrochloride was added to the mixture and agitated to dissolution. The mixture was diluted to 16 L and cooled to 30 °C. 909.2 g of dextrose was added to the mixture and agitated to dissolution. The mixture was adjusted with sodium hydroxide to a final pH of 3.5. The solution was then diluted to 20 L with distilled, deionized water. This provided a solution having an approximate drug concentration of 1.8 mg/mL.

Example 2: Preparation of Amiodarone Formulation Using Methanesulfonic Acid

To a 100 mL beaker was added 30 mL of distilled, deionized water. To this was added 0.1 g of amiodarone hydrochloride. The mixture was brought to 45-60°C in a hot water bath. The

mixture was pH adjusted with methanesulfonic acid and sodium hydroxide (if necessary) to a pH of 3 - 4.5. (At this point, an osmotic agent such as dextrose, mannitol and glycerol, may optionally be added if desired, and mixed until dissolved) The solution was then diluted to 50 mL with distilled, deionized water. The final concentration of amiodarone hydrochloride was approximately 2 mg/mL.

Formulation Stability

Formulations prepared as described above were found to be stable with respect to drug concentration, pH, and visual particulate when refrigerated or frozen over a 1 year period in glass.

These formulations also passed the USP particle limits for parenteral products.

While the specific embodiments have been illustrated and described, numerous modifications come to mind without significantly departing from the spirit of the invention and the scope of protection is only limited by the scope of the accompanying claims.

CLAIMS

We claim:

1. A parenteral solution for intravenous administration without the necessity of dilution comprising: an active ingredient, amiodarone, in a concentration range from 0.2 to 10 mg/ml and a pH modifying solution selected from the group consisting of lactate buffer, lactic acid, methanesulfonate buffer and methanesulfonic acid, and any combination thereof, the solution having a pH within the range from approximately 2.5 - 4.5.

2. The solution of claim 1 wherein the pH modifying solution is lactic acid.

3. The solution of claim 1 wherein the pH modifying solution is a lactate buffer.

4. The solution of claim 1 wherein the pH modifying solution is methanesulfonic acid.

5. The solution of claim 1 wherein the pH modifying solution is methanesulfonate.

6. The solution of claim 1 further comprising an osmotic agent.

7. The solution of claim 6 wherein the osmotic agent is selected from the group consisting of dextrose, mannitol, sorbitol, glycerol, amino acids such as glycine, and inorganic salts such as sodium chloride.

8. A method for preparing an amiodarone intravenous solution for intravenous administration comprising the steps of:

providing an effective ingredient of amiodarone;

providing distilled water;

providing an acid selected from the group consisting of lactic acid and methanesulfonic acid or combinations thereof;

mixing an effective amount of the acid, the distilled water and the amiodarone to define a solution;

adjusting the pH of the solution to be within the range of from approximately 2.5 - 4.5;

and

adjusting the concentration of the amiodarone to be within the range of from about 0.2 to about 25 mg/ml.

9. The method of claim 8 further comprising: providing an osmotic agent selected from the group consisting of dextrose, mannitol, sorbitol, glycerol, amino acid, and inorganic salt, or any combination thereof, and mixing the osmotic agent into the solution.

10. The method of claim 8 wherein the step of mixing the acid, the amiodarone and the distilled water comprises the step of heating the solution to a temperature from about 45°C to about 70°C.

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